

I claim:

1. An agent, comprising:

- 5 (a) a clostridial neurotoxin, or component thereof, attached to;
(b) a targeting moiety,

wherein the targeting moiety is selected from the group consisting of transmission compounds, and compounds substantially similar to the transmission compounds.

10

2. The agent of claim 1, wherein the transmission compound can be released by a neuron to transmit or to facilitate the transmission or the generation of a pain signal.

15 3. The agent of claim 1, wherein the clostridial neurotoxin includes neurotoxins as well as derivatives and fragments of neurotoxins made by a *Clostridial beratti*, *Clostridial butyricum*, *Clostridial botulinum* or *Clostridial tetani* bacterium.

20 4. The agent of claim 1, wherein the clostridial neurotoxin component is derived from botulinum toxin selected from the group consisting of botulinum toxin types A, B, C, D, E, F, G and mixtures thereof.

25 5. The agent of claim 1, wherein the clostridial neurotoxin component includes at least

one of a heavy chain, a fragment of a heavy chain, a light chain and a fragment of a light chain.

5 6. The agent of claim 5, wherein the fragment of a heavy chain or the light chain includes at least one of a carboxyl end segment and an amine end segment.

7. The agent of claim 4, wherein the clostridial neurotoxin comprises at least a part of a
10 heavy chain and at least a part of a light chain of a clostridial neurotoxin, the heavy chain being derived from one botulinum toxin serotype and the light chain being derived from a different botulinum toxin serotype.

15 8. The agent of claim 1, wherein the clostridial neurotoxin component comprises a light chain or a fragment of a light chain linked to a heavy chain or to a fragment of a heavy chain by a direct covalent linkage.

20 9. The agent of claim 1, wherein the clostridial neurotoxin has a light chain or a fragment of a light chain linked to a heavy chain or a fragment of a heavy chain by one or more spacer components.

25 10. The agent of claim 1, wherein the transmission compound is selected from the group consisting of amino acids, substituted counterparts thereof and mixtures thereof.

11. The agent of claim 10, wherein the transmission compound is selected from a group consisting of glutamates, substituted counterparts thereof and mixtures thereof.

5

12. The agent of claim 10, wherein the amino acids are linked to form at least one peptide.

10 13. The agent of claim 12, wherein at least one peptide is a tachykinin.

14. The agent of claim 13, wherein the tachykinin is substance P.

15

15. The agent of claim 12, wherein at least one peptide is selected from a group consisting of natural precursors of substance P and synthetic precursors of substance P.

20

16. The agent of claim 12, wherein at least one peptide is selected from the group consisting of fragments of substance P.

25 17. The agent of claim 12, wherein at least one peptide is selected from the group

consisting of substance P analogues comprising at least one D-amino acid and substance P analogues comprising a disulfide bridge.

5 18. The agent of claim 1, wherein the clostridial neurotoxin is covalently attached to the targeting moiety.

19. The agent of claim 1, wherein the clostridial neurotoxin is covalently coupled to the
10 targeting moiety through one or more spacer components.

20. The agent of claim 14, wherein the clostridial neurotoxin comprises a light chain linked to a fragment of a heavy chain, wherein the heavy chain is derived from an amine
15 end segment of a heavy chain of a botulinum neurotoxin toxin type A and the targeting moiety comprises Substance P.

21. A method for obtaining an agent for alleviating pain, the method comprising:

- 20 (a) producing a genetic construct having codes for a clostridial neurotoxin or component thereof selected from the group consisting of a clostridial neurotoxin, a modified clostridial neurotoxin and fragments thereof;
- (b) incorporating the construct into a host organism;
- (c) expressing the construct to produce the clostridial neurotoxin component; and
- 25 (d) covalently attaching the clostridial neurotoxin to a targeting moiety selected from the group consisting of transmission compounds released from neurons in transmitting pain

Sub B1
signals and components substantially similar to the transmission compounds.

22. The method of claim 21, wherein the covalent linkage includes one or more spacer
5 components.

23. A method for obtaining an agent for treating pain, the method comprising:

(a) producing a genetic construct having codes for (1) a clostridial neurotoxin

Sub B1
10 component selected from a group consisting of clostridial neurotoxin, a modified
clostridial neurotoxin and fragments thereof and (2) a targeting moiety selected from the
group consisting of transmission compounds released from neurons in transmitting pain
signals and components substantially similar to the transmission compounds;

(b) incorporating the genetic construct into a host organism; and

15 (c) expressing the genetic construct to obtain a fusion protein comprising the clostridial
neurotoxin components covalently coupled to the targeting moiety.

24. The method of claim 23, wherein the genetic construct includes genetic codes that
20 encode for a spacer component between the clostridial neurotoxin component and the
targeting moiety.

25. The method of claim 23, wherein the targeting moiety is substance P.

26. An polypeptide agent for alleviating pain, the agent comprising:

(a) a first amino acid sequence region comprising:

(i) a first domain, the first domain comprising a targeting moiety, the targeting moiety being selected from the group consisting of transmission compounds released from neurons in transmitting pain signals and compounds substantially similar to the transmission compounds; and

(ii) a second domain, the second domain comprising a translocation element able to facilitate the transfer of the polypeptide across an endosome membrane, and

b) a second amino acid sequence region comprising a therapeutic element having biological activity or therapeutic activity when released into the cytoplasm of a target cell.



27. The polypeptide of claim 26, wherein the second domain of the first amino acid sequence region comprises a clostridial neurotoxin heavy chain or derivative or fragment thereof.

28. The polypeptide of claim 27, wherein the clostridial neurotoxin heavy chain is derived from a *Clostridial botulinum* neurotoxin type A.

29. The polypeptide of claim 27, wherein the second amino acid sequence region comprises a clostridial neurotoxin light chain.

30. The polypeptide of claim 29, wherein the clostridial neurotoxin light chain is derived from *Clostridial botulinum* neurotoxin type A.

5 31. The polypeptide of claim 27, wherein the clostridial neurotoxin heavy chain is derived from *Clostridial tetani* neurotoxin.

32. The polypeptide of claim 27, wherein the clostridial neurotoxin heavy chain is
10 derived from an organism selected from the group consisting of *Clostridial botulinum* type B, C, D, E, F and G; *Clostridial baratii*; and *Clostridial butyricum*.

33. The polypeptide of claim 26, wherein the first domain comprises a targeting moiety
15 able to bind surface receptors of spinal cord neurons under physiological conditions.

34. The polypeptide of claim 33, wherein the second domain comprises a clostridial neurotoxin light chain.

20

35. The polypeptide of claim 26, wherein the targeting moiety specifically binds a receptor on a spinal cord dorsal horn neuron.

25

36. A plasmid encoding a polypeptide that is derived from a clostridial neurotoxin,

Sub
B1

comprising:

a) a first nucleotide sequence region comprising;

5 i) a first portion encoding an amino acid sequence region comprising a targeting moiety that is (1) selected from a group consisting of transmission compounds released from neurons in transmitting pain signals and components substantially similar to the transmission compounds, and (2) able to specifically bind to receptors on cells under physiological conditions; and

10 ii) a second portion encoding an amino acid sequence region comprising a translocation element able to facilitate the transfer of a polypeptide across an endosome membrane; and

b) a second nucleotide sequence region encoding an additional amino acid sequence region comprising a therapeutic element having biological activity when released into the cytoplasm of a target cell, and an origin of replication directing plasmid replication by a host cell.

15

37. A method of making a polypeptide derived from a clostridial neurotoxin comprising:

(a) inserting the plasmid of claim 36 into a suitable host cell,

(b) growing the host cell in culture, and

20 (c) permitting the host cell to express the polypeptide from the plasmid.

38. A method for treating pain, the method comprising the step of administration to a human patient of a therapeutically effective amount of an agent, wherein the agent
25 comprises a clostridial neurotoxin component coupled to a targeting moiety selected from a group consisting of transmission compounds released from neurons in transmitting pain signals and components substantially similar to the transmission

compounds.

39. The method of claim 38, wherein the clostridial neurotoxin component is derived
5 from botulinum toxin selected from the group consisting of botulinum types A, B, C, D,
E, F, G and mixtures thereof.

40. The method of claim 39, wherein the clostridial neurotoxin component comprises a
10 light chain and an amine end segment of a heavy chain.

41. The method of claim 40, wherein the targeting moiety comprises substance P.

15 42. The method of claim 39, wherein the agent contains botulinum toxin in an amount
between about 10^{-3} U/kg and about 35 U/kg.

43. The method of claim 39, wherein the agent contains botulinum toxin in an amount
20 between about 1 U/kg and about 10 U/kg.

44. The method of claim 39, wherein the agent contains botulinum toxin in an amount
about 3 U/kg.

45. The method of claim 39, wherein the agent contains botulinum toxin in an amount between about 1 U and about 500 U.

5

46. The method of claim 39, wherein the agent contains botulinum toxin in an amount between about 10 U and about 300 U.

10 47. The method of claim 39, wherein the agent contains botulinum toxin in an amount about 70 U.



15 48. The method of claim 38, wherein the pain alleviating effect persists for from about 2 to about 6 months.

49. The method of claim 38, wherein the agent is administered locally at the periphery.

20

50. The method of claim 49, wherein the agent is administered intramuscularly.

51. The method of claim 38, wherein the agent is administered intrathecally.

25

52. The method of claim 38, wherein the agent is administered intrathecally to a cranial region of the central nervous system.

5

53. The method of claim 38, wherein the agent is administered intrathecally to a cervical region of the central nervous system.

10 54. The method of claim 38, wherein the agent is administered intrathecally to a thoracic region of the central nervous system.

15 55. The method of claim 38, wherein the agent is administered intrathecally to a lumbar region of the central nervous system.

56. The method of claim 38, wherein the agent is administered intrathecally to a sacral region of the central nervous system.

20

57. The method of claim 38, wherein the administration step includes the steps of:
(a) accessing a subarachnoid space of a central nervous system of a mammal, and;
(b) injecting the agent into the subarachnoid space.

25

58. The method of claim 57, wherein the accessing step is carried out by effecting a spinal tap.

5

59. The method of claim 38, wherein a administration step includes the steps of:

(a) catheterization of a subarachnoid space of the central nervous system of a mammal, and;

10 (b) injecting the agent through a catheter inserted by the catheterization step into the subarachnoid space.

60. The method of claim 59, wherein the administration step includes, prior to the injecting step, the step of attaching to or implanting in the mammal an administration
15 means for administering the agent to the central nervous system of the mammal, the administration means comprising a reservoir of the agent, the reservoir being operably connected to a pump means for pumping an aliquot of the agent out of the reservoir and into an end of the catheter in the subarachnoid space.

20

61. The method of claim 38, wherein the administration step is carried out prior to the onset of a nociceptive event or syndrome experienced by the mammal.

25 62. The method of claim 61, wherein the administration step is carried out before to about 14 days before the onset of the nociceptive event.

63. The method of claim 38, wherein the administration step is carried out after the onset of a nociceptive event.

5

64. The method of claim 63, wherein the nociceptive event is a neuropathic pain syndrome.

10

65. The method of claim 63, wherein the nociceptive event is inflammatory pain.

66. An agent for treating pain, the agent comprising:

15

- (a) a botulinum toxin type A proteolytic domain attached to ;
- (b) a botulinum toxin type A translocational domain, and
- (c) substance P attached to the translocational domain.

add.